AMERICAN UNIVERSITY OF BEIRUT

BISPHENOL A EXPOSURE ASSESSMENT FROM OLIVE OIL CONSUMPTION

by
TAREK FAYEZ ABOU OMAR

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TAREK FAYEZ ABOU OMAR

Approved by:

Dr. Hassan Dhaini, Assistant professor, Department of Environmental Health	Advisor
Dr. Rima Habib, professor and Chair, Department of Environmental Health	Member of Committee
Dr. Mohamad G. Abiad, Associate professor, Department of Nutrition and Food Sciences	Member of Committee

Date of project presentation: November 4, 2016

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The use of Bisphenol A (BPA) in packaging material has grown extensively over the past 50 years despite concerns of its migration into packaged foods and beverages, resulting in human exposure. Many studies have reported tumorigenic effects and endocrine alterations associated with BPA exposure in animal models. This study aims at assessing human exposure to BPA from olive oil. A total of 27 olive oil samples were collected from mills and local villagers in the District of Hasbaya, a major olive oil harvesting region in Lebanon. Information on storage conditions was also collected using a standard questionnaire. BPA was extracted and quantified by High-Performance Liquid Chromatography (HPLC). Results showed significantly higher BPA levels in olive oil samples stored in plastic vs. non- plastic packaging (mean = 333 vs. 150 µg/kg, p-value = 0.006), in samples with a plastic storage duration of >1 year compared to those with a storage duration of < 1 year (mean = 452 vs. 288 µg/kg, p-value = 0.008), and in oil samples sourced from locals compared to oil mills (mean = 376 vs. 228 µg/kg, p-value = 0.022). Statistically significant higher BPA levels remained for samples stored in plastic vs. non-plastic packaging in the bootstrap multivariable linear regression (B = 144.23, 95%CI: 67.85-252.07), while storage duration was the only significant variable (B=163.58, 95% CI: 51.38-263.47, p-value = 0.03). The estimated exposure was found to be 1.38 % of the tolerable daily intake (TDI) as established by the European Food Safety Agency (EFSA). This is the first report on BPA levels in Mediterranean olive oil. Further studies are needed to complete a more accurate exposure assessment accounting for BPA exposure from various sources and studying its contribution to existing epidemics in the country.

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ABREVIATIONS

BPA: Bisphenol A

CI: Confidence interval, SE: Standard error

EDC: Endocrine Disrupter

EFSA: European Food Safety Agency

EDI: Estimated daily intake

ECHA: European Chemical Agency

HDPE: High Density polyethylene

HDPP: High Density polypropylene

HPLC: High Performance liquid chromatography

LDPE: Low Density Polyethylene

LOQ: Limit of Quantification

PET: Polyethylene terephthalate

PVC: Polyvinyl chloride

PC: Polycarbonate

PS: polystyrene

SPSS: Statistical Analysis Software Package

TDI: Tolerable daily intake

CHAPTER 1

INTRODUCTION

Bisphenol A (BPA) is a heavily produced industrial chemical on a global scale (Vandenberg et al. 2010). Over 6 billion pounds are produced annually (Burridge, 2003). BPA is commonly used as a monomer in polycarbonate plastic containers of food and beverages, as well as a non-polymer additive in several consumer products including plastic toys, thermal paper, cigarette filters, water pipes, tableware, electronics, and dental fillers (Biedermann et al. 2010, Huang et al. 2012, Welshons et al. 2006). BPA is also found in epoxy resins as protective lining for canned foods and as coating on lids of beverages and drinks (World Health Organization 2009).

Humans are exposed to BPA through multiple routes, but most importantly through ingestion as a result of migration from the package into food and beverages (Geens et al. 2012, Groff 2010). Several studies have reported detectable levels of BPA in urine, serum, umbilical cord blood, and breast milk, both in developed and developing countries, revealing widespread human exposure to this contaminant (Calafat et al. 2008, Rochester 2013). Since BPA is rapidly metabolized in the body (Volkel et al. 2002), the high frequency detection indicates repeated exposure among studied populations.

Olive oil is a major component of Mediterranean diet. Historically, olive and olive oil were stored in pottery and glass containers; however, in the last decade, plastic containers started replacing pottery and glass as lighter, more practical, and cheaper alternatives. In Lebanon, local farmers, mills' owners, and villagers in the District of Hasbaya have also started using plastic containers for transporting and storing olive oil. In this study we investigated olive oil storage conditions in the District of Hasbaya, a major olive oil harvesting region in Lebanon, and quantified the levels of olive oil BPA in the aim of assessing human exposure.

CHAPTER 2

LITERATURE REVIEW

2.1 Health effects of BPA

BPA is classified as an endocrine disrupter chemical (EDC) by several regulatory agencies (Vandenberg et al. 2012). This classification is based on a large number of studies reporting BPA's ability to interact with several endocrine receptors (Chapin et al. 2008). Exposure to BPA is thought to be associated with higher risk of prostate and breast cancer, diabetes, and cardiovascular diseases, based on numerous studies in rodents (Gupta 2000, Lang et al. 2008, Murray et al. 2007). In addition, BPA is associated with developmental and reproductive adverse effects (Bredhult et al. 2007; Tsutsumi, 2005), and neurobehavioral alterations (Vom Saal et al. 2007). BPA displays a pleiotropic effect with non-monotonic dose-response at significantly low doses (Wetherill et al. 2007). Recently, the European Chemical Agency (ECHA) decided to classify BPA as a "Category 1B Reproductive Toxicant" as an alarming substance for human sexual function and fertility (European Food Safety 2015b). Based on these new data and methodologies, the European Food Safety Agency (EFSA) lowered the tolerable daily intake (TDI) to 4 µg/Kg-w/day. The new estimated safe level is twelve and a half times lower than the previously allowed level of 50 µg/Kg-BW/day (European Food Safety 2015a). This decision is based on building evidence of adverse effects at doses several times lower than the estimated safe levels and based on the BPA non-monotonic dose-response behavior. These new regulatory restrictions on BPA highlight the importance of investigating human exposure from all possible sources in order to achieve an accurate human health risk assessment.

2.2 Migration of BPA from plastics

According to the European Union regulation Number 10/2011 on plastics and materials intended to have contact with food and beverages, the acceptable migration limit of BPA is 0.6 mg/kg. (Torres et al. 2015). One of the most important sources of human exposure to BPA is through packaged food (Kang et al, 2006; Chapin et al, 2008). Exposure to BPA from nonfood sources is generally very minimal or less likely to happen (Geens et al. 2012). Several studies have shown that migration from plastic packaging does occur under specific environmental conditions such as variation in temperature, humidity and light (Tawfik and Huyghebaert, 1999). In a study testing the migration of BPA from epoxy resins to canned tomatoes, all samples contained BPA levels close to 0.4 µg/kg except those that were exposed to high temperature and longer storage durations (Errico et al. 2014). The presence of BPA in PC packaged food and water is well established in the literature. Several studies have shown that migration of BPA is occurring from HDPE, HDPP and PET packaging into food, beverages, and drinking water. BPA has been identified and quantified in milk packaged in HDPE bottles in concentrations between 0.28 and 2.64 µg/kg (Casajuana & Lacorte, 2004). It was also detected in PC, HDPE, LDPE, and polystyrene (PS) plastics (Guart et al. 2011). Besides migration, other studies have reported that oil can induce swelling in plastic which would increase the migration process (Kassouf et al. 2014). At the same time, plastic packages have the ability to absorb different volatile and nonvolatile compounds from food via scalping (Kiritsakis et al. 2002).

CHAPTER 3

MATERIALS AND METHODS

3.1 Samples and Data collection

A comprehensive list of all oil mills in the District of Hasbaya, Lebanon, was obtained from the database of the Lebanese Ministry of Environment. Out of the 31 identified olive oil mills 14 were sampled whilst the remaining olive oil mills were either permanently closed or out of stock at the time of the study. In addition, 13 random olive oil samples were collected from local distributors within the same geographical location (Figure 1). Pre-scheduled onsite visits to the mills and distributors were conducted, during which information on storage conditions, including temperature, humidity, exposure to light and oxygen, and type of packaging, were obtained. At each site, representative olive oil samples were collected both from plastic and non-plastic containers, when available, and from containers with different storage durations. In order to avoid contamination, a stainless steel ladle was rinsed with methanol and deionized water prior to sampling. Depending on the type of container, oil was either sampled utilizing the ladle or directly dropped into glass bottles and stored at 4 ^{o}C until laboratory analysis was conducted.

Figure 1- Satellite view of sampling locations in the District of Hasbaya (Scale: 1.5 cm = 2 km)

3.2 BPA Extraction and quantification by HPLC

In order to extract BPA, olive oil was stirred to allow homogenization. For each 5g of olive oil, 15 ml of n-hexane were added, using a volumetric cylinder, then mixed thoroughly. 2 ml of methanol: water (1:1) were then added to each sample, mixed for 1 min using a mechanical shaker, and left for 30 min to allow the separation of phases (Franz and Rijk 1996). The obtained lower aqueous phase was then filtered using syringe filtration (0.2 μm Filter) into an Alltech HPLC Vial for injection (Alltech Associates Inc., FL, USA).

An Agilent 1100 series HPLC system (Santa Clara, CA, USA) was used for analysis. The HPLC column used was: Ods Hypersil stainless steel 250 x 4, 6 mm packed with C18 coated spherical silica gel, particle size 5 μm. For a stringent validation, three standard curves were developed. For quantification, a standard curve was constructed using the following spikes: 0; 0.1; 0.3; 0.5; 1; and 2 ppm, from a BPA standard (Bisphenol A > 99%, Sigma-Aldrich cat# 239658), and to a blank (BPA-free olive oil sample from a stain steel container). A volume of 20 μL of the extract was injected into the HPLC system. The detection of BPA was achieved at 5.3 min through a fluorescence detector (excitation wavelength 225 nm and emission wavelength 310nm). The mobile phase used was methanol: water (70:30) at a flow rate of 1ml/min.

3.3 Quality assurance and control

Since BPA is abundant in the environment, contact with plastic materials was avoided during sample collection, extraction, and analysis. For quality control, one blank, one duplicate, and one spike were performed for each 10 samples. The limit of quantification (LOQ) was measured three times by spiking BPA-free olive oil and hexane with 0.3ppm BPA. BPA levels in blanks were below detection limit. Analytical BPA levels below detection limit were set equal to

LOQ divided by 2. The standard curve was linear over the selected points (correlation coefficient $R^2 = 0.9966$).

3.4 Statistical analysis

Descriptive statistics (mean, median, standard deviation, counts and percentages) were used to summarize the study variables. BPA levels were computed and compared across duration of storage and packaging type using the non-parametric Mann-Whitney U test. Variables that were significant in the multivariable analysis were included in a multivariable linear regression model. Due to the small sample size, the non-parametric bootstrap technique was used to estimate the standard error (SE), p-value and 95% confidence interval (CI) for the regression coefficients. In the bootstrap analysis, 1000 samples of the same size as the original sample were drawn, with replacement from the original data set. Statistical analyses were conducted using the Statistical Analysis Software Package (SPSS Statistics 24, IBM Corporation, NY, USA). A *p*-value of less than 0.05 was considered statistically significant.

CHAPTER 4

FINDINGS

4.1 Sample characteristics

A total of 27 oil samples were collected, 14 (52%) of which were obtained from oil mills and the rest from local distributors. Twenty two (82%) were kept in plastic packages, 20 (74%) for less than one year, 24 (89%) were kept under room temperature and 18 (67%) in dark storage rooms (Table 1). Collected oil samples from plastic containers were distributed as following: 6 samples from high density polyethylene (HDPE) containers, 3 samples from polyethylene, 1 sample from polypropylene (PP), and 12 samples from unspecified types. Out of 27 samples 17 were above the detection limit, 5 out of 6 stored in HDPE, 3 out of 3 in PE, 1 out of 1 PP and 8 out of 12 unspecified types of plastic containers (Figure 2).

Figure 2: Sample distribution across plastic containers

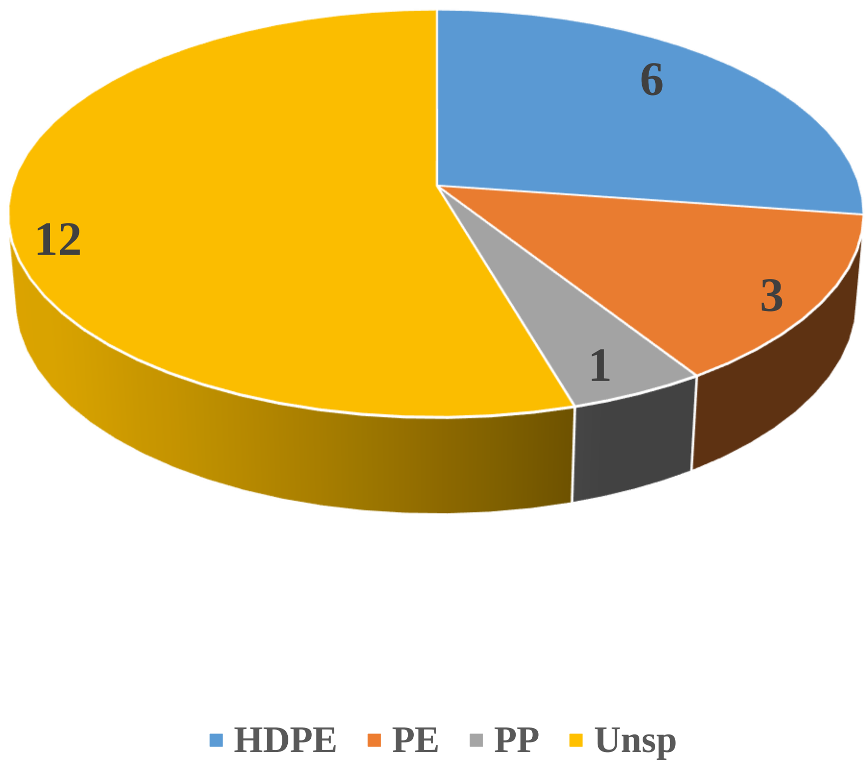

Table 1 - Distribution of BPA levels across storage and packaging categories

	BPA (μg/Kg)					
	N	(%)	Mean	Median	Standard Deviation	P-value
Variable						
Supplier						
Oil Mill	14	(51.9)	228.14	150.00	103.81	
Locals	13	(48.1)	376.15	358.00	181.01	0.022*
Packaging						
Plastic	22	(81.5)	333.36	323.00	160.95	
Non-Plastic	5	(18.5)	150.00	150.00	0.00	0.006*
Temperature						
Cool	3	(11.1)	270.33	254.00	129.28	
Room temperature	24	(88.9)	303.04	254.00	167.42	0.914
Storage in Darkness						
Yes	18	(66.7)	329.89	287.00	167.59	
No	9	(33.3)	238.44	150.00	138.43	0.139
Storage Duration**						
< 1 year	16	(72.7)	288.75	254.00	160.31	
>=1 year	6	(27.3)	452.33	458.00	91.37	0.008*

*P<0.05
** The effect of storage duration on BPA levels was assessed among plastic containers only (N = 22)

4.2 Unadjusted associations of BPA levels with study variables

Significantly higher BPA levels were found in oil samples obtained from plastic containers compared to non-plastic (mean = 333 vs. 150 µg/kg, p-value = 0.006), and in those obtained from local distributors compared to those obtained from oil mills (mean = 376 vs. 228 µg/kg, p-value = 0.022) (Table 1). Among samples stored in plastic (N=22), significantly higher levels of BPA were found in oil samples stored for more than 1 year compared to those stored for less than one year (mean = 452 vs. 288 µg/kg, p-value = 0.008) (Table 1).

4.3 Bootstrap multivariable linear regression

Two multivariable linear regression models were carried out. In the first, for the total sample (N=27), significantly higher BPA levels were observed in olive oil samples stored in plastic containers (B=121.56, 95% CI: 53.44 -194.39, p-value = 0.009). In the second, for the samples stored in plastic containers (N=22), storage duration was the only significant variable (B=163.58, 95% CI: 51.38-263.47, p-value = 0.03).

CHAPTER 5

DISCUSSION

Despite evidence of adverse effects, environmental monitoring and exposure assessment of BPA is still incomplete. Previous studies have reported potential migration of BPA to olive oil from different types of plastic packaging (Kassouf et al. 2014, Lopez-Cervantes and Paseiro-Losada 2003). Our study is the first report documenting BPA in Mediterranean olive oil. Exposure to BPA through consumption of olive oil is assessed using the highest detected level (0.78 µg/g) in order to characterize the maximum individual risk. At an assumed olive oil daily intake of 5g (Nasreddine et al. 2006) for an adult weighing 70 Kg, the estimated daily intake (EDI) of BPA from olive oil is (0.055 µg/kg/day). This level of exposure only contributes to 1.375 % of the EFSA TDI. At the same time, it is important to note that the suggested EDI of 5g/day may be an underestimation since it is restricted to consumption of olive oil used as topping (Nasreddine et al. 2006). In fact, olive oil is used in many regions of Lebanon in cooking and frying as well. In European countries on the Mediterranean coast; however, the average daily consumption of olive oil is reported to be much higher. In Greece, the average daily intake of olive oil is estimated to be 40.6 g/day for men and 29.4 g/day for women, whereas in Italy the average consumption for men is estimated to be 20.7 g/day and 15.2 g/day for women (Buckland and Gonzalez 2010). Assuming a BPA contamination of 0.78 µg/g (the highest detected level in our study), the projected EDI of BPA from olive oil in Greece would be 0.452 µg/kg/day. The level of exposure would still only contribute to 11.31 % of the EFSA TDI.

We had previously conducted an exposure assessment for BPA from polycarbonate bottled water in Lebanon and reported an estimated BPA daily ingestion of 0.046 µg/Kg/day for adults and 0.20 µg/Kg/day for infants (Dhaini and Nassif 2014). The combined exposure from both plastic packaged olive oil and PC bottled water in Lebanon would amount to 0.102 µg/Kg/day, hence remains under the TDI established by the EFSA (2.55% of TDI).

The statistically significant differences in BPA levels we found between plastic and non-plastic packaged olive oil (mean = 333 vs. 150 µg/Kg) and those between short-term and long-term stored olive oil (mean= 288 µg/Kg vs. 452 µg/Kg) clearly suggest that oil contamination is due to the gradual migration of BPA from various plastic packaging over time. Our findings may be explained by polymer degradation during storage (Vandenberg et al. 2007). Previous studies have reported a significant migration of the biologically active BPA from polycarbonate plastic into packaged beverages due to overuse of containers (Brede et al. 2003). In addition, several studies have shown that migration of plasticizers not only occurs from polycarbonate plastic, but also from high density polyethylene (HDPE) and high density polypropylene (HDPP) plastic under specific environmental conditions such as variation in temperature, humidity, and light (Tawfik and Huyghebaert 1999). Global migration of different plasticizers, including polyethylene terephthalate (PET), polyvinylchloride (PVC), polypropylene (PP), and polystyrene (PS), into different types of vegetable oils, including olive oil, may start 1-2 months after storage at room temperature (Tawfik 2005). One study showed that olive oil stored in PP containers for more than 10 days at 44^{o}C contained PP molecules in amounts close to 10 mg/dm^2 (Wang and Storm 2006). More importantly, BPA was found in PC, HDPE, PS, and low-density polyethylene (LDPE), (Guart et al. 2011). On the other hand, another study demonstrated the ability of olive oil to induce swelling in plastic, hence speeding up the migration process (Kassouf et al. 2014). The interaction between olive oil and the plastic package may actually be a two-way process. The plastic package does have the ability to absorb volatile and nonvolatile substances from olive oil in a process known as scalping (Kiritsakis et al. 2002). On the other hand, the significant differences in BPA levels we found between samples from oil mills and those from locals may be attributed to the fact that oil mills acquire new plastic containers each season in order to sell their product, while a significant number of locals have either reusable large old barrels and/or small timeworn tanks.

Much of the scientific interest in BPA is related to evidence suggesting that it is an EDC. EDCs act by interacting with molecules participating in biosynthesis, secretion, action, or metabolism of hormones (Diamanti-Kandarakis et al. 2009). BPA is described as a "weak" xenoestrogen based on its ability to bind estrogen receptors, and to interact with the thyroid receptor, and the androgen receptor (Kuiper et al. 1998). Recent attention to the developmental effects of BPA is based on animal studies. Exposure to BPA during pregnancy and lactation resulted in reduced birth weight, slowed growth, reduced survival, and delayed puberty (Kim et al. 2001, Tyl et al. 2008). Evidence for adverse effects in animals exposed during gestation or lactation were reported at considerably low BPA doses (2-20 μg/Kg/day) (Ayyanan et al. 2011, Richter et al. 2007). Other studies have found an association between prenatal/perinatal BPA exposure and neurological effects, insulin resistance, as well as a higher risk of breast and prostate tumors (Alonso-Magdalena et al. 2006, Ho et al. 2006). The developmental alterations in mammary glands were actually reported at BPA doses as low as 0.025 μg/Kg (Munoz-de-Toro et al. 2005, Wadia et al. 2007). Based on a critical review, the US National Toxicology Program (NTP) recognized the existence of: (1) some concern for BPA adverse effects on the brain, behavior, and prostate of fetuses and infants; (2) minimal concern for effects on the mammary gland and puberty in females; and (3) negligible concern for fetal/neonatal mortality, birth defects, and reduced birth weight (National Toxicology Program 2008).

This study has a few limitations. First, the dietary exposure assessment may be underestimated due to other potential sources of BPA not accounted for. We have tried to overcome this limitation by estimating a combined exposure from both olive oil and drinking water based on previous reports (Dhaini and Nassif 2014). Other potential dietary sources of exposure, such as metallic lining of aluminum cans and other EDCs such as phthalates alkyl-phenols should be further investigated in this population to achieve a more accurate risk assessment. Second, potential seasonal variations in BPA levels –due to fluctuation in temperature- were not examined in this study. However, we did compare differences in BPA levels in packaged olive oil of short and long-term durations and reported statistically significant differences. Third, this study is not tied with any human study to examine potential associations between exposure and health risks. Despite these limitations, we showed solid evidence of BPA migration into packaged olive oil over time. Our findings should be complemented with future epidemiological studies aiming at investigating the overall BPA contribution to epidemics in the population, particularly infertility, developmental alterations, and current patterns of breast cancer and incidence of prostatic diseases.

CHAPTER 6

CONCLUSIONS AND RECOMMEDNDATIONS

In summary, this study highlights BPA as a ubiquitous dietary contaminant. Although levels detected were below the current EFSA's TDI, however, concerns about potential health risks persist based on recurrent evidence of a low-dose effect for BPA. Moreover, several scientists challenge the use of TDI for risk assessment on EDCs (vom Saal and Welshons 2006). Their argument is based on the effects of EDCs observed at low doses, the reported non-monotonic dose-response curves, as well as the observed effects in *in utero* exposure (Diamanti-Kandarakis et al. 2009). In addition, controversy continues over the biological significance of many of the more sensitive endpoints and studies that only assessed conventional toxicity and overlooked potential effects on sexual function and fertility. A better understanding of the mechanism of action of BPA with the different target molecules will improve reliability of the health risk assessment. We recommend regulating packaging and storage of olive oil, a significant constituent of the Mediterranean diet, in order to protect consumers in Lebanon and in Mediterranean countries.

APPENDIX

Olive Oil Sampling Sheet

<table>
<tr><td colspan="3">Geographic Location:______________________________

○ Oil Mill Storage (specify name): ___________________________
○ Locals Storage</td></tr>
<tr><td colspan="2">Type of Packaging:

○ Plastic
○ Glass
○ Stainless steel
○ Other</td><td>If Plastic, please specify the following:

Type_______________________________

Expiration Date________________________

Source of Container____________________</td></tr>
<tr><td colspan="3">Storage Conditions</td></tr>
<tr><td>Duration

○ 0-3 months
○ 3-12 months
○ 1-2 years
○ More than 2 years</td><td>Temperature

○ Cool
○ Room Temperature
○ Heated

Temperature in degrees C:</td><td>Exposed to Oxygen (open-air or loose capping)

○ Yes
○ No</td></tr>
<tr><td>Humidity:

○ Yes</td><td>Stored in the Dark

○ Yes</td><td>Comments:</td></tr>
</table>

<table>
<tr><td>○ No

Actual measure:</td><td colspan="2">○ No</td><td></td></tr>
<tr><td colspan="2">**Oil Sample(s) Obtained**

○ **Yes**
○ **No**</td><td colspan="2">**Sample Code:___________________________**

Date of Sampling (DD-MM-YY)___________

Signature_______________________________</td></tr>
<tr><td colspan="4"></td></tr>
</table>

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